

NOV 22 2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of Enina Fishman
Serial No. 09/700,751 Group Art Unit: 1623
Filed: January 4, 2001 Examiner: J. Young
For: PHARMACEUTICAL COMPOSITIONS COMPRISING AN
ADENOSINE..

DECLARATION
under Rule 132

Commissioner of Patents and Trademarks
Washington, D.C. 20231

I, Ad P. IJzerman, a Dutch citizen residing at Park
Oosterspaarn 6, 2036MB Haarlem, The Netherlands, hereby
declare:

1. I am Professor at the Leiden/Amsterdam Center for
Drug Research at Leiden University in Leiden, The
Netherlands. I am a medicinal chemist with expertise in
the field of adenosine receptors.
2. My Curriculum Vitae and list of publications is
attached herewith as Annex "A".
3. I have reviewed the patent application in re, serial
number 09/700,751 which relates to the use of A
adenosine receptor agonists, among other for treating
cancer.
4. I am familiar with the manuscript of Mittelman, A.
et al (1975) Annals N.Y. Acad. Sci. 225:225-234
(hereinafter "Mittelman"), which relates, among others,
to the compound N⁶-(A² isopentenyl)adenosine
(hereinafter "IPA").
5. IPA, a bodily substance, is an N⁶-substituted
adenosine derivative. The corresponding adenine
derivative (without the ribose) is a plant cytokinin.

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From a literature search I conducted (for manuscripts considered see "Annex B") it appears that IPA has been shown to be active on certain tumor cell lines, with quite a few references to the L-1210 leukemia cell line. None of the manuscripts I considered refer to adenosine receptors to explain the compound's mechanism of action. In fact, it was believed that IPA interferes with methionine metabolism.

6. In conclusion, to me the use of an A_2 adenosine receptor agonist in treating cancer is new and not anticipated by the abovementioned Mittelman manuscript. This is corroborated by the fact that the first mentioning of an adenosine A_2 receptor was only in the early nineties (Meyerhof et al, FEBS Lett. 1991,284:155-160; Zhou et al, Proc Natl Acad Sci U S A 1992,89:7432-7436; these references are attached as Annexes "C" and "D", respectively).

7. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date, June 29, 2004



Dr. An Ijzerman

Annex A

CURRICULUM VITAE DR. A. P. IJZERMAN

Name: Adriaan Pieter IJzerman
Date of Birth: 23 December 1954
Place of Birth: Heemstede, The Netherlands

Education

- 1975 Bachelor's degree in pharmaceutical sciences (Utrecht University)
1979 Master's degree in pharmaceutical sciences (specialisation medicinal chemistry, Utrecht University)
1980 Qualification as a pharmacist (Utrecht University)
1985 Ph.D. degree in medicinal chemistry (Free University of Amsterdam, promoter Prof. dr. H. Timmerman)

Present Employment

Professor of medicinal chemistry at Leiden University, Leiden/Amsterdam Center for Drug Research, division of medicinal chemistry (area: receptor research/molecular modelling; website: www.medchem.leidenuniv.nl). He supervises a research group currently consisting of 2 assistant professors, 2 post-doctoral fellows, 5 Ph.D. students, and 3 technicians. He also served as a professor of receptor medicinal chemistry at the Vrije Universiteit in Amsterdam (1998-2002).

He has acted as a copromoter to the following theses.

- A. Garritsen, Molecular pharmacology of the adenosine A₁ receptor, 1990
- P.J.M. van Galen, Adenosine receptors: structural requirements for agonists and antagonists, 1990
- A. van der Bent, Cholecystokinin A receptor antagonists - a medicinal chemistry approach, 1993
- A.M. van Rhee, P₂-purinergic receptors - a quest for selective and competitive antagonists, 1993
- E.M. van der Wenden, Structural requirements for the interaction between ligands and the adenosine A₁ receptor, 1994
- M.W. Beukers, Extracellular breakdown of ATP by human blood cells, 1995
- R.A.A. Mathôt, Preclinical pharmacokinetic-pharmacodynamic modelling of the cardiovascular effects of adenosine receptor ligands, 1995

- B. van Steen, Structure-affinity relationship studies on 5-HT_{1A} receptor ligands, 1996
W. Kuipers, Receptor-ligand interactions of G protein-coupled receptors - the 5-HT_{1A} receptor as a model, 1996
E.A. van Schaick, Selectivity of adenosine receptor agonists in vivo, 1997

As a promoter he has been involved with the following theses.

- K. Ingkaninan, Novel procedures for lead finding in plant extracts, 2000
M. de Zwart, Ligands for the human adenosine A_{2B} receptor, 2000
Z-G Gao, Allosteric modulation of G protein-coupled receptors, 2000
E. van Tilburg, Novel partial agonists for adenosine receptors, 2001
J.E. van Muijlwijk-Koezen, Antagonists for the human adenosine A₃ receptor, 2001
M. Schrier, Adenosine and apoptosis in neuroblastoma cells, 2002
A.F. de Lig, Adenosine A₁ receptors: Constitutive activity, inverse agonism and allosteric modulation, 2003
T.J.H. Bueters, Treatment of organophosphate poisoning with adenosine A₁ receptor agonists, 2003
M.P. Schaddelee, Adenosine A₁ receptor agonists. Blood-brain barrier transport and PK/PD correlations in neuropathic pain, 2003

Research Experience

1980-1985

Ph.D. research and thesis, entitled "The beta-adrenoceptor complex. Requirements for the interaction with its ligands."

1985-today

within the division of medicinal chemistry research is focussed on purinergic (adenosine) receptors and nucleoside transport proteins. These proteins are tools in the broader perspective of the main theme of research, viz. the understanding of the mechanisms of interaction between a small molecule (i.e., a drug, a hormone, a neurotransmitter) and receptor proteins.

Awards

1979 research award Utrecht University

1987 Millipore Science Education Award

1997 Rottendorf-Europa-Preis

2000 Science Teaching Award (Leiden University)

2001 "Tulip-and-Oak" medal, presented at the 13th
Noordwijkerhout-Camerino Symposium

2001 Nomination Leiden University Best Teacher

2003 Nomination Leiden University Best Teacher

Publications

Dr. IJzerman is the (co)author of approx. 150 publications in international scientific journals. He lectured upon invitation at numerous conferences.

Further Scientific Activities

- Member of the board of the medicinal chemistry division of the Royal Dutch Chemical Society (1989 - 1995)
- Member of the board of the Dutch Pharmacological Society (1997-2001)
- Member of the Scientific Chapter to the New Drug Research Foundation (1997-1999)
- Member of STIGON (promotion of start-up pharmaceutical business initiatives) (1999-2003)
- Chairman of FIGON (Dutch Federation for Innovative Drug Research) (2000-2004)
- Member of the IUPHAR adenosine receptor nomenclature committee (1997-today)
- Referee to
 - Molecular Pharmacology
 - Journal of Medicinal Chemistry
 - Biochemical Pharmacology
 - European Journal of Medicinal Chemistry
 - European Journal of Pharmacology
 - European Journal of Pharmaceutical Sciences
 - Drug Design and Discovery
 - Drug Development Research
 - Pharmaceutical Research
 - General Pharmacology
 - Neurochemistry International
 - Life Sciences
 - Nucleosides & Nucleotides
 - Journal of Neurochemistry
 - Journal of Pharmacology and Experimental Therapeutics
 - Journal of Receptor Research & Signal Transduction
 - Receuil des Travaux Chimiques des Pays-Bas
 - Environmental Toxicology and Pharmacology
 - PROTEINS: Structure, Function, and Genetics

Journal of Ethnopharmacology
Journal of Chemical Crystallography
British Journal of Pharmacology
Neuropharmacology
Bioorganic & Medicinal Chemistry
Bioorganic & Medicinal Chemistry Letters
Trend in Pharmacological Sciences
Journal of Controlled Release
Genomes
Brain Research
FEBS Letters
Tetrahedron

- Chairman of the organisation committee and member of the scientific committee of the international symposium "Pharmacology of purinergic receptors. Implications for drug design" (Noordwijk, 6 - 8 July 1990)
- Member of the organisation committee of the 6th International Conference on Retinal Proteins (Leiden, 19 - 24 June 1994)
- Organiser of LACDR 'School on medicinal chemistry', Noordwijkerhout, October 27 - 30, 1992; October 26 - 29, 1993; October 25 - 28, 1994; October 24 - 27, 1995, October 22 - 25, 1996; October 27 - 30, 1997; October 27-30, 1998; October 26-29, 1999; October 24-27, 2000; October 23-26, 2001; October 22-25, 2002; October 28-31, 2003.
- Chairman of the organisation and scientific committee of the international workshop on Inverse Agonism, Barcelona, June 22-24, 2000
- Chairman of the organisation committee of the Esteve symposium on Inverse Agonism, Hostal de S'Agaro, October 2-5, 2002
- Member of the scientific and organisation committees of several congresses and symposia organised by various Dutch bodies
- Member of several election committees for full professorships in the Netherlands
- Scientific advisor at the NIH/NIDDK, Bethesda, USA (May/June 1991)
- Participant in several courses on 'research management' and 'human resource management'
- Member of the editorial board of Drug Development Research (1992-today)
- Member of the editorial board of Drug Design and Discovery (1992-1997)
- Member of the editorial board of Molecules (an electronic journal) (1999-today)
- Member of the editorial board of Drug Design and Reviews - Online (2003-today)
- Programme Coordinator of granted EC BIOMED concerted action 'Adenosine receptors in the brain (ADEURO)' (1994-1996)

- Managing co-director of granted EC BIOTECH programme 'Molecular mechanisms of beta-adrenergic receptor function and regulation (EUROCEPTOR)' (1993-1996)
- Managing co-director in granted EC BIOTECH programme 'An advanced data management system for G protein-coupled receptors (GPCRDB)' (1996-1999)
- Programme coordinator of granted EC BIOMED programme 'Inverse agonism. Implications for drug design' (1997-2000)

Publications of Dr. IJzerman

- Wilting J, Kremer JMH, IJzerman AP, Schulman SG.
The kinetics of the binding of warfarin to human serum albumin as studied by stopped-flow spectrophotometry.
Biochim. Biophys. Acta 706, 96 - 104 (1982).
- IJzerman AP, Bultsma T, Timmerman H, Zaagsma J.
The ionization of beta-adrenoceptor ligands: a method for unravelling ionization schemes.
J. Pharm. Pharmacol. 36, 11 - 15 (1984).
- IJzerman AP, Bultsma T, Timmerman H, Zaagsma J.
The relation between ionization and affinity of beta-adrenoceptor ligands.
Naunyn-Schmiedeberg's Arch. Pharmacol. 327, 293 - 298 (1984).
- IJzerman AP, Dorlas R, Aué GHJ, Timmerman H.
Factors controlling beta₁-adrenoceptor affinity and selectivity.
Biochem. Pharmacol. 34, 2883 - 2890 (1985).
- IJzerman AP, Aué GHJ, Bultsma T, Linschoten MR, Timmerman H.
Quantitative evaluation of the beta₂-adrenoceptor affinity of phenoxypropanolamines and phenylethanolamines.
J. Med. Chem. 28, 1328 - 1334 (1985).
- IJzerman AP.
The beta-adrenoceptor complex. Requirements for the interaction with its ligands (Ph. D. thesis).
Elinkwijk BV, Utrecht, 1985.
- Linschoten MR, Bultsma T, IJzerman AP, Timmerman H.
Mapping the turkey erythrocyte beta-receptor: a distance geometry approach.
J. Med. Chem. 29, 278 - 286 (1986).
- IJzerman AP, Bultsma T, Timmerman H.
Quantitative evaluation of the beta₂-adrenoceptor intrinsic activity of N-tert.butyl phenylethanolamines.
J. Med. Chem. 29, 549 - 554 (1986).
- IJzerman AP, Bultsma T, Timmerman H.
Binding characteristics of the regulatory guanine nucleotide binding protein, and the activation of the enzyme adenylate cyclase, present in a bovine skeletal muscle membrane preparation.
Res. Comm. Chem. Pathol. Pharmacol. 52, 93 - 105 (1986).
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The beta-adrenoceptor complex (abstract of Ph. D. thesis).
Pharmaceut. Weekbl. Sci. Ed. 8, 155 - 157 (1986).

IJzerman AP, Timmerman H.
The beta-adrenoceptor/adenylate cyclase complex. From model to biochemical reality (review).
Pharmaceut. Weekbl. Sci. Ed. 8, 209 - 222 (1986).

Severne Y, IJzerman AP, Nerme V, Timmerman H, Vauquelin G.
Shallow agonist competition binding curves for beta-adrenergic receptors: the role of tight agonist binding.
Mol. Pharmacol. 31, 69 - 73 (1987).

Galen PJM v, IJzerman AP, Soudijn W.
Adenosine derivatives with N⁶-alkyl, -alkylamine or -alkyladenosine substituents as probes for the A₁-receptor.
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IJzerman AP, Nagesser A, Garritsen A.
The membrane stabilizing activity of β -adrenoceptor ligands.
Biochem. Pharmacol. 36, 4239 - 4244 (1987).

Garritsen A, IJzerman AP, Soudijn W.
[³H]Batrachotoxinin-A 20- α -benzoate binding to sodium channels in rat brain: sensitivity to tetrodotoxin and divalent cations.
Eur. J. Pharmacol. 145, 261 - 266 (1988)

IJzerman AP.
Receptor models and mechanisms. Perspectives for new drugs.
Pharmaceut. Weekbl. 123, 378 - 382 (1988)

Debing I, IJzerman AP, Vauquelin G. Melanosome binding and oxidation - reduction properties of synthetic l-DOPA-melanine as in vitro tests for drug toxicity.
Mol. Pharmacol. 33, 470 - 476 (1988)

IJzerman AP, Vlijmen HWT v.
A molecular graphics study exploring a putative ligand binding site of the β -adrenoceptor.
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Pharmaceut. Res. 5, 772 - 775 (1988)

IJzerman AP, Soudijn W.
The antiarrhythmic action of beta-adrenoceptor antagonists (review).
TIPS 10, 31 - 36 (1989)

Galen PJM v, Leusen FJJ, IJzerman AP, Soudijn W.
Mapping the N⁶-region of the adenosine-A₁ receptor using
computer graphics.
Eur. J. Pharmacol. 172, 19 - 27 (1989)

Garritsen A, IJzerman AP, Soudijn W.
Adenosine A₁ receptors are not coupled to Ca²⁺ uptake in rat
brain synaptosomes. Biochem. Pharmacol. 38, 693 - 695 (1989)

IJzerman AP, Menkveld GJ, Thedinga KH.
A refined method for the photoaffinity labelling of the
nucleoside transport protein: application to cell membranes of
calf lung tissue. Biochim. Biophys. Acta 979, 153 - 156 (1989)

Pirovano IM, IJzerman AP, Galen PJM v, Soudijn W.
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adenosines on adenosine receptor affinity and intrinsic
activity.
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Vlijmen HWT v, IJzerman AP.
Molecular modeling of a probable ligand binding site on the β -
adrenergic receptor.
J. Comp. Aid. Molec. Des. 3, 165 - 174 (1989)

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Inhibition of nucleoside transport by a new series of compounds
related to lidoflazine and mioflazine. Eur. J. Pharmacol. 172,
273 - 281 (1989)

Galen PJM v, IJzerman AP, Soudijn W.
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further evidence for adenosine's anti mode of binding.
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receptor based on steric, electrostatic and hydrophobic
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for the interaction with PIA, DPCPX and amiloride.
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transport inhibitors.
Naunyn-Schmiedeberg's Arch. Pharmacol. 342, 336 - 341 (1990)

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TIPS 11, 342 - 343 (1990)

Pirovano IM, Van Belle H, IJzerman AP.
Inhibition of nucleoside uptake in human erythrocytes by a new series of compounds related to lidoflazine and mioflazine.
Eur. J. Pharmacol. - Mol. Pharmacol. Sect. 189, 419 - 422 (1990)

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J. Med. Chem. 34, 1202 - 1206 (1991)

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Receptor binding profiles of amiloride analogues provide no evidence for a link between receptors and the Na⁺/H⁺ exchanger, but indicate a common structure on receptor proteins.
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Recognition of adenosine receptors by amiloride and its analogues.
Nucleosides & Nucleotides 10, 1107 - 1111 (1991)

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Nucleosides & Nucleotides 10, 1039 - 1047 (1991)

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A model for the hydrogen bonding interactions between adenosine receptor ligands and histidyl residues in the adenosine A₁ receptor binding site, based on AM1 calculations.
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Mapping the C8-region of the adenosine A₁ receptor with computer graphics.
Eur. J. Pharmacol. - Mol. Pharmacol. Sect. 206, 315 - 323 (1991)

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Kinetics, ultrastructural aspects and molecular modelling of transdermal peptide flux enhancement by N-alkylazacycloheptanones.
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binding site on the A₁ receptor.
Drug Design and Discovery 9, 49 - 67 (1992)

Van Galen PJM, Melman N, IJzerman AP, Jacobson KA.
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Structural analysis of kappa-opioid receptor agonists
Recl. Trav. Chim. Pays-Bas 112, 169 - 173 (1993)

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Binding of the radioligand [³⁵S]adenosine-5'-O-(2-
thiodiphosphate) and intracellular calcium response in rat
liver parenchymal cells.
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Drug Dev. Res. 28, 237 - 243 (1993)
- Mathôt RAA, Appel S, Van Schaick EA, Soudijn W, IJzerman AP, Danhof M.
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Synthesis and biological evaluation of lorglumide-like hybrid cholecystokinin-A receptor antagonists.
Drug Development Research 31, 197 - 205 (1994)
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Nucleoside transport inhibition and platelet aggregation in human blood: R75231 and its enantiomers, draflazine and R88016.
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Pharmacological analysis of ecto-ATPase inhibition: evidence for combined enzyme inhibition and receptor antagonism in P_{2x}-purinoceptor ligands.
Br. J. Pharmacol. 113, 1432 - 1438 (1994)
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Pharmacokinetic-pharmacodynamic relationship of the cardiovascular effects of the adenosine A_1 receptor agonist N^6 -cyclopentyladenosine (CPA) in the rat.
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TIPS 15, 311-312 (1994)

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Drug Design & Discovery 12, 129 - 148 (1994)

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Partial agonism of theophylline-7-ribose on adenosine receptors.
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In: Adenosine and adenine nucleotides: from molecular biology to integrative physiology (Belardinelli L and Pelleg A, eds),
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